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REVIEW

The prognosis of mid-range ejection fraction heart failure: a systematic review and meta-analysis

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Abstract

Aims Mid-range ejection fraction is a new entity of heart failure (HF) with undetermined prognosis till now. In our systematic review and meta-analysis, we assess the mortality and hospitalization rates in mid-range ejection fraction HF (HFmrEF) and compare them with those of reduced ejection fraction heart failure (HFrEF) and preserved ejection fraction HF (HFpEF).

Methods and results We conducted our search in March 2018 in the following databases for relevant articles: PubMed, CENTRAL, Google Scholar, Web of Science, Scopus, NYAM, SIEGLE, GHL, VHL, and POPLINE. Our primary endpoint was assessing all-cause mortality and all-cause hospital re-admission rates in HFmrEF in comparison with HFrEF and HFpEF. Secondary endpoints were the possible causes of death and hospital re-admission. Twenty-five articles were included in our meta-analysis with a total of 606 762 adult cardiac patients. Our meta-analysis showed that HFmrEF had a lower rate of all-cause death than had HFrEF [relative risk (RR), 0.9; 95% confidence interval (CI), 0.85–0.94]. HFpEF showed a higher rate of cardiac mortality than did HFmrEF (RR, 1.09; 95% CI, 1.02–1.16). Also, HFrEF had a higher rate of non-cardiac mortality than had HFmrEF (RR, 1.31; 95% CI, 1.22–1.41).

Conclusions We detected a significant difference between HFrEF and HFmrEF regarding all-cause death, and non-cardiac death, while HFpEF differed significantly from HFmrEF regarding cardiac death.

Keywords Heart failure with mid-range ejection fraction; Mortality; Hospitalization; Meta-analysis

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Introduction

Left ventricular ejection fraction (LVEF) has long been used in the stratification of patients with HF, although it is not an ideal parameter owing to its relative subjectivity. The lack of evidence supporting the use of other parameters such as myocardial deformation imaging made LVEF widely accepted for stratifying HF patients.[1]

Considering LVEF, there are three types of heart failure (HF); the largest is the reduced ejection fraction (HFrEF) (EF $<$ 40%), which is widely distributed, and the smallest is the preserved ejection fraction (HFpEF) (EF $>$ 50%).[2] Although HFpEF was considered in the literature only two decades ago, it proved that almost half of HF patients fall in this category with an expected rise in the future.[3] Between these two types, there is the mid-range ejection fraction (HFmrEF) (EF 40–49%), which is considered as a grey zone according to the European Society of Cardiology guidelines.[2,4]

Although few studies described HFmrEF prevalence in comparison with that of other HF types, HFmrEF proved to have intermediate clinical picture, haemodynamics, laboratory findings, and echocardiographic data between the other two types.[1,5–7]

In 2017 and depending on a registry report, the mortality rates of HFmrEF, HFrEF, and HFpEF were reported[8]; however, a stronger evidence is needed to estimate the rate difference.

In our meta-analysis, we measured all-cause mortality, cardiac mortality, non-cardiac mortality, all-cause hospitalization, and HF-related hospitalization in HFmrEF in comparison with HFrEF and HFpEF to better understand the differences between the three subgroups and to determine the features of HFmrEF.

Methods

The study is written according to the guidelines and recommendations in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[9] No published protocol for this systematic review and meta-analysis exists.

Literature search strategy

We conducted a systematic search in PubMed, CENTRAL, Google Scholar, Web of Science, Scopus, NYAM, SIEGLE, GHL, VHL, and POPLINE using the terms *mid-range ejection fraction heart failure*, *mid-range ejection fraction heart failure*, *borderline ejection fraction heart failure*, *HFmrEF*, *prognosis*, *mortality*, *death*, and *re-admission*. We conducted this search in December 2017, and it was updated in March 2018.

Study selection

Studies were eligible if (i) they aimed at defining the prognosis of HFmrEF in terms of mortality and hospitalization, (ii) they included patients (adult men or women) aged >18 years old with no restriction to the date of publication, and (iii) the studies defined HF subtypes according to the European Society of Cardiology guidelines (HFrEF as <40%, HFmrEF as 40–49%, and HFpEF as ≥50%).[2,4] We did not include studies not restricting to this guideline for fear of data overlap between the HF subtypes.Reviews, comments, duplicated publications, non-English articles, articles with unreliable data extraction, and pooling analyses of original studies were excluded. After including the eligible articles, we manually searched the reference lists of these studies for relevant articles.

Data extraction and quality assessment

The following data were extracted: (i) study characteristics like study title, year of publication, study design, country of study, inclusion criteria of the patients, total sample size, number of patients in each category of HF, their ages, and their gender male percentage; and (ii) criteria of the study outcomes like all-cause mortality, cardiac mortality, non-cardiac mortality, all-cause hospitalization, and HF-related hospitalization.

The methodological quality of included studies was appraised using National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.[10] The score consists of 14 questions covering the assessment of the study methodology. A study was given one or zero points according to its fulfilment of the conditions. The total score was 14 points, and a study with a score ≥ 10 points was considered of high quality.

Statistical analysis

The study measures included all-cause mortality, cardiac mortality, non-cardiac mortality, all-cause hospitalization, and HF-related hospitalization.

All statistical analyses were performed with the REVMAN software (version 5.3; Cochrane Collaboration, Oxford, UK). The Mantel–Haenszel method was used to calculate estimates, confidence intervals (CIs), and *P* values. Statistical heterogeneity was tested with the I^2 statistic, with $I^2 \leq 50\%$ indicating no significant heterogeneity.[11] In case of significant heterogeneity, a random effect model was used, while a fixed effect model was used in case of no significant heterogeneity. Relative risk (RR) was calculated from raw published study data, and all outcomes were reported with a 95% CI. For the χ^2 test, a P value < 0.05 was considered statistically significant.

Results

Search results

As shown in *Figure 1*, we identified 299 records in the preliminary search. After scanning the titles or abstracts and removing the duplicates, we excluded 238 articles. The remaining 61 publications underwent full-text screening, of which 42 failed to meet the inclusion criteria and were removed. On data extraction, 23 articles were excluded. On manual searching of the reference lists of the remaining 19 articles, we found another six articles to include. Finally, 25 articles were included in the final data analysis.[3,8,12–34]

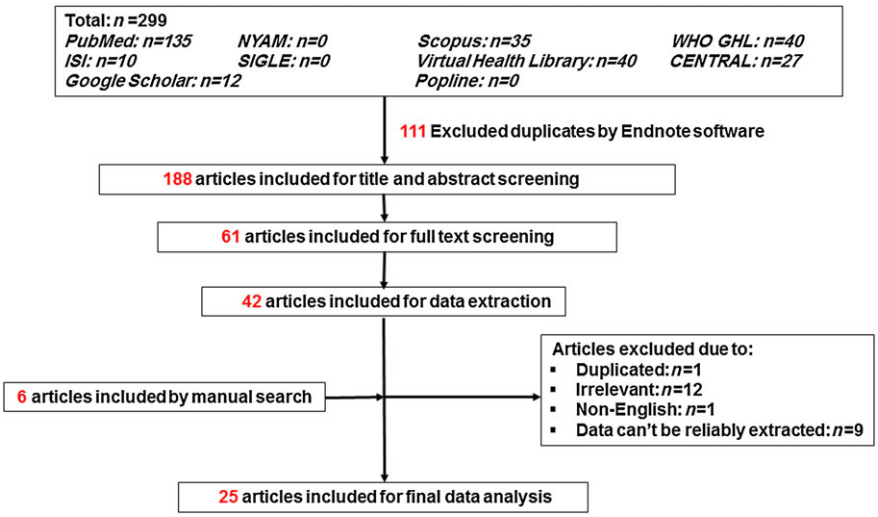
Study characteristics

As shown in *Table 1*, the set of eligible studies consists of 10 prospective cohort studies and 15 retrospective studies with a total of 606 762 patients. The included studies were published from 2001 to 2018. The period of follow-up ranged from 1 month to 5 years, and the most common adjusted variables were age and sex. Regarding the quality of the studies, the NIH scores ranged from 9 to 13 with a mean of 11.2, suggesting the presence of high methodological quality.

All-cause death

As shown in *Figure 2*, HFmrEF had a significantly lower all-cause death rate than had HFrEF (RR, 0.9; 95% CI, 0.85–

Figure 1 Flow chart showing the number of included papers after literature search, title/abstract screening, full text screening, data extraction, and final data analysis.



0.94; $P < 0.001$). On the other hand, there was no significant difference between HFpEF and HFmrEF (RR, 0.98; 95% CI, 0.86–1.12; $P = 0.82$). Both analyses detected high levels of heterogeneity ($I^2 = 84\%$ and $I^2 = 98\%$).

Cardiac and non-cardiac mortality rates

As shown in *Figure 3*, the pooled analyses of the cardiac mortality results showed no significant difference between HFrEF and HFmrEF (RR, 0.89; 95% CI, 0.69–1.15; $P = 0.38$), but HFpEF had a significantly higher cardiac mortality rate than had HFmrEF (RR, 1.09; 95% CI, 1.02–1.16; $P = 0.001$). The two pooled analyses detected low levels of heterogeneity ($I^2 = 0\%$ and $I^2 = 46\%$).

Regarding the non-cardiac mortality results, HFrEF had a significantly higher rate than had HFmrEF (RR, 1.31; 95% CI, 1.22–1.41; $P < 0.001$), while there was no significant difference between HFpEF and HFmrEF (RR, 0.91; 95% CI, 0.75–1.09; $P = 0.3$). The analyses showed low and high levels of heterogeneity ($I^2 = 46\%$ and $I^2 = 57\%$).

All-cause and HF-related hospitalization

As shown in *Figure 4*, the pooled analyses of all-cause hospitalization showed no significant difference between HFrEF and HFmrEF or between HFpEF and HFmrEF (RR, 0.91; 95% CI, 0.18–4.59; $P = 0.9$; and RR, 0.95; 95% CI, 0.84–1.07; $P = 0.38$, respectively). Both analyses detected high levels of heterogeneity ($I^2 = 100\%$ and $I^2 = 62\%$).

Regarding HF-related hospitalization, the pooled analyses showed also no significant differences between HFrEF and HFmrEF or between HFpEF and HFmrEF (RR, 0.92; 95% CI, 0.84–1.01; $P = 0.08$; and RR, 1.05; 95% CI, 0.83–1.33; $P = 0.69$, respectively). Both analyses had high levels of heterogeneity ($I^2 = 85\%$ and $I^2 = 98\%$).

Discussion

For a decade now, it has been uncertain as to whether HFmrEF should be considered as a separate clinical entity of HF and subsequently having different prognosis and treatment from HFpEF and HFrEF or not; so, in our study, we measured the mortality rates and hospital re-admission rates in the different types as a measure of this difference.

Moher *et al.*[9] and Gomez-Otero *et al.*[12] considered HFmrEF as part of HFrEF owing to its high prevalence of ischaemic heart disease and its response to N terminal pro-brain natriuretic peptide-guided therapy. On the other hand, Margolis *et al.*[13] and Coles *et al.*[14] considered HFmrEF as a separate clinical entity with intermediate features between HFrEF and HFpEF.[13,14]

Some studies suggested that HFmrEF represents a transitional status or an overlap zone between HFpEF and HFrEF, rather than an independent entity of HF, and another study showed that HFmrEF constitutes intermediate features between both HFpEF and HFrEF, with more similarities towards HFpEF than to HFrEF.[35]

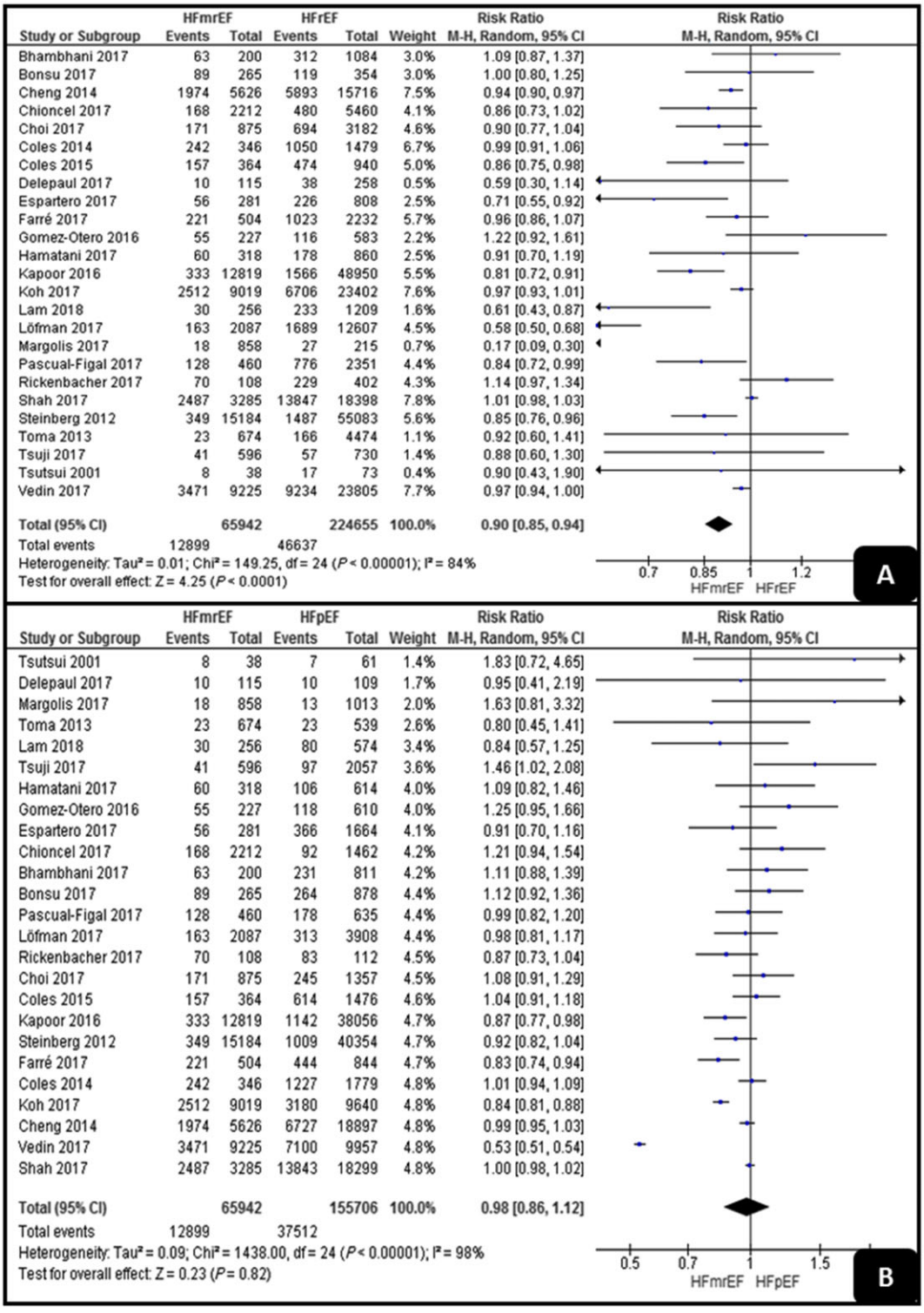
Morbidity and mortality rates proved to be similar in HFpEF and HFrEF[36]; however, there are not enough studies to measure them in HFmrEF. On the other hand, there are many studies discussing all-cause mortality, HF-related

Table 1 Study characteristics and the patient characteristics in the included studies

Study	Publication year	Patients' country	Design	Total sample size	HFrEF			HFmrEF			HFpEF		
					Number	Age (years)	% men	Number	Age (years)	% men	Number	Age (years)	% men
Lam *et al*.	2018	New Zealand and Singapore	Prospective cohort	2039	1209	62.1 ± 13.2	83	256	65.8 ± 12.7	69	574	71.5 ± 11.8	52
Hamatani *et al*.	2018	Japan	Retrospective cohort	1792	860	—	—	318	—	—	614	—	—
Guisado-Espartero *et al*.	2018	Spain	Prospective cohort	2735	808	79 (72–84)	62	281	80 (74–84)	58	1664	81 (76–86)	37
Vedin *et al*.	2017	Sweden	Retrospective cohort	42 789	23 805	—	70	9225	—	64	9957	—	45
Shah *et al*.	2017	USA	Retrospective cohort	39 982	18 398	79 (73–85)	59	3285	81 (74–86)	49	18 299	82 (75–87)	33
Rickenbacher *et al*.	2017	Switzerland	Retrospective cohort	622	402	75.5 ± 7.5	67	108	79 ± 6.8	53	112	80.2 ± 7.1	35
Pascual-Figal *et al*.	2017	Spain	Retrospective cohort	3446	2351	64.4 ± 12.3	76.8	460	66.7 ± 12.1	73	635	72.1 ± 12.2	42.8
Margolis *et al*.	2017	Israel	Prospective cohort	2243	215	67 ± 15	78	858	62 ± 13	79	1013	60 ± 12	81
Choi *et al*.	2018	Korea	Prospective cohort	5625	3182	—	—	875	—	—	1357	—	—
Koh *et al*.	2017	Sweden	Retrospective cohort	42 061	23 402	72 ± 12	71	9019	74 ± 12	60	9640	77 ± 11	45
Gomez-Otero *et al*.	2017	Spain	Retrospective cohort	1420	583	68.2 ± 12.8	76.7	227	72.5 ± 11.1	67	610	75 ± 10.7	46.7
Farré *et al*.	2017	Spain	Prospective cohort	3580	2232	66.2 ± 12.5	75.7	504	68.1 ± 12.9	66.9	844	73.5 ± 11.4	44
Delepaul *et al*.	2017	France	Prospective cohort	482	258	66 ± 12	72	115	69 ± 13	72	109	71 ± 12	55
Chioncel *et al*.	2017	22 countries	Prospective cohort	9134	5460	64 ± 12.6	78	2212	64.2 ± 14.2	68.5	1462	68.6 ± 13.7	52
Bonsu *et al*.	2017	Ghana	Prospective cohort	1488	354	58.9 ± 14.2	48.1	265	60.4 ± 12.7	50.2	878	60.8 ± 14.6	43.3
Bhambhani *et al*.	2017	USA	Prospective cohort	28 820	1084	70 ± 10	64	200	72 ± 8	52	811	71 ± 9	41
Coles *et al*.	2015	USA	Retrospective cohort	4025	940	71.4	60	364	74.4	45.1	1476	75.7	33
Coles *et al*.	2014	USA	Retrospective cohort	3604	1479	73.7 ± 12.8	56.5	346	76.1 ± 11.4	45.4	1779	76.5 ± 11.9	33.4
Cheng *et al*.	2014	USA	Retrospective cohort	40 239	15 716	79 (72–85)	60	5626	81 (74–86)	49.5	18 897	82 (75–87)	32.7
Tsuji *et al*.	2017	Japan	Retrospective cohort	3480	730	66.9 ± 12.7	76.7	596	69.0 ± 11.6	71.8	2154	71.7 ± 10.9	60.8
Steinberg *et al*.	2012	USA	Retrospective cohort	110 621	55 083	70 (58–80)	64	15 184	76 (65–84)	53	40 453	78 (67–85)	37
Toma *et al*.	2014	398 centres across the world	Retrospective cohort	5687	4474	64 (54–73)	71.4	674	73 (64–81)	58.9	539	76 (66–82)	41.6
Kapoor *et al*.	2016	USA	Retrospective cohort	99 825	48 950	69.6 ± 14.2	63.2	12 819	74.4 ± 13.3	51.1	38 056	75.9 ± 13.1	34.9
Löfman *et al*.	2017	Sweden	Retrospective cohort	40 230	12 607	67 (59–76)	75	2087	71 (62–79)	47.5	3908	75 (65–82)	51
Tsutsui *et al*.	2001	Japan	Prospective cohort	172	61	67 ± 14	71	38	69 ± 9	61	73	69 ± 16	49

Numbers are expressed as mean ± SD or median (inter-quartile range).

Figure 2 Forest plots demonstrating all-cause death in (A) HFrEF and HFmrEF and (B) HFpEF and HFmrEF. HFmrEF, mid-range ejection fraction heart failure; HFpEF, preserved ejection fraction heart failure; HFrEF, reduced ejection fraction heart failure.



mortality, all-cause hospital re-admission, and HF-related hospital re-admission, so we pooled these outcomes to better understand this new entity of HF.[2]

Our meta-analysis is the largest study meta-analysing the results of HFmrEF prognosis in the elderly population. Our study further supports the European Society of Cardiology

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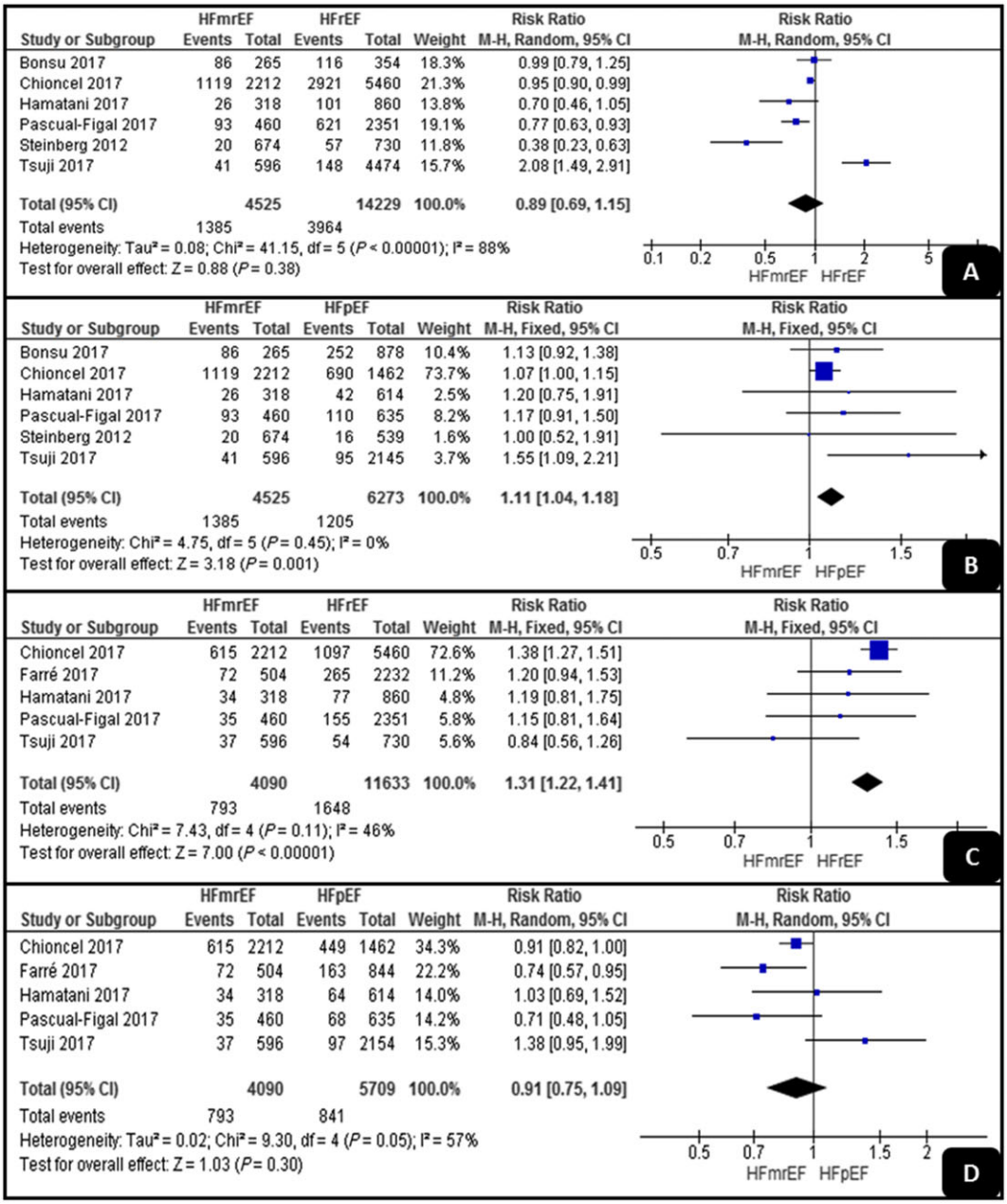
Figure 3 Forest plots demonstrating (A, B) cardiac and (C, D) non-cardiac mortality rates. HFmrEF, mid-range ejection fraction heart failure; HFpEF, preserved ejection fraction heart failure; HFrEF, reduced ejection fraction heart failure.



guidelines by showing a significant difference between HFmrEF and HFrEF or HFpEF. This further supports the guidelines considering HFmrEF as a separate entity. Our meta-analysis detected a significant difference between HFrEF and HFmrEF regarding all-cause death and non-cardiac death, but there was no difference between the two arms regarding cardiac mortality, all-cause hospitalization, or HF-related hospitalization. On the other hand, we detected a significant difference between HFpEF and HFmrEF regarding cardiac mortality, but there was no significant difference between the two arms regarding all-cause death, non-cardiac mortality, all-cause hospitalization, or HF-related hospitalization.

These findings further support the statistical evidence making it a separate entity, but the clinical significance of HFmrEF separation must be reconsidered as only few of the outcomes significantly differed between the HF subtypes,

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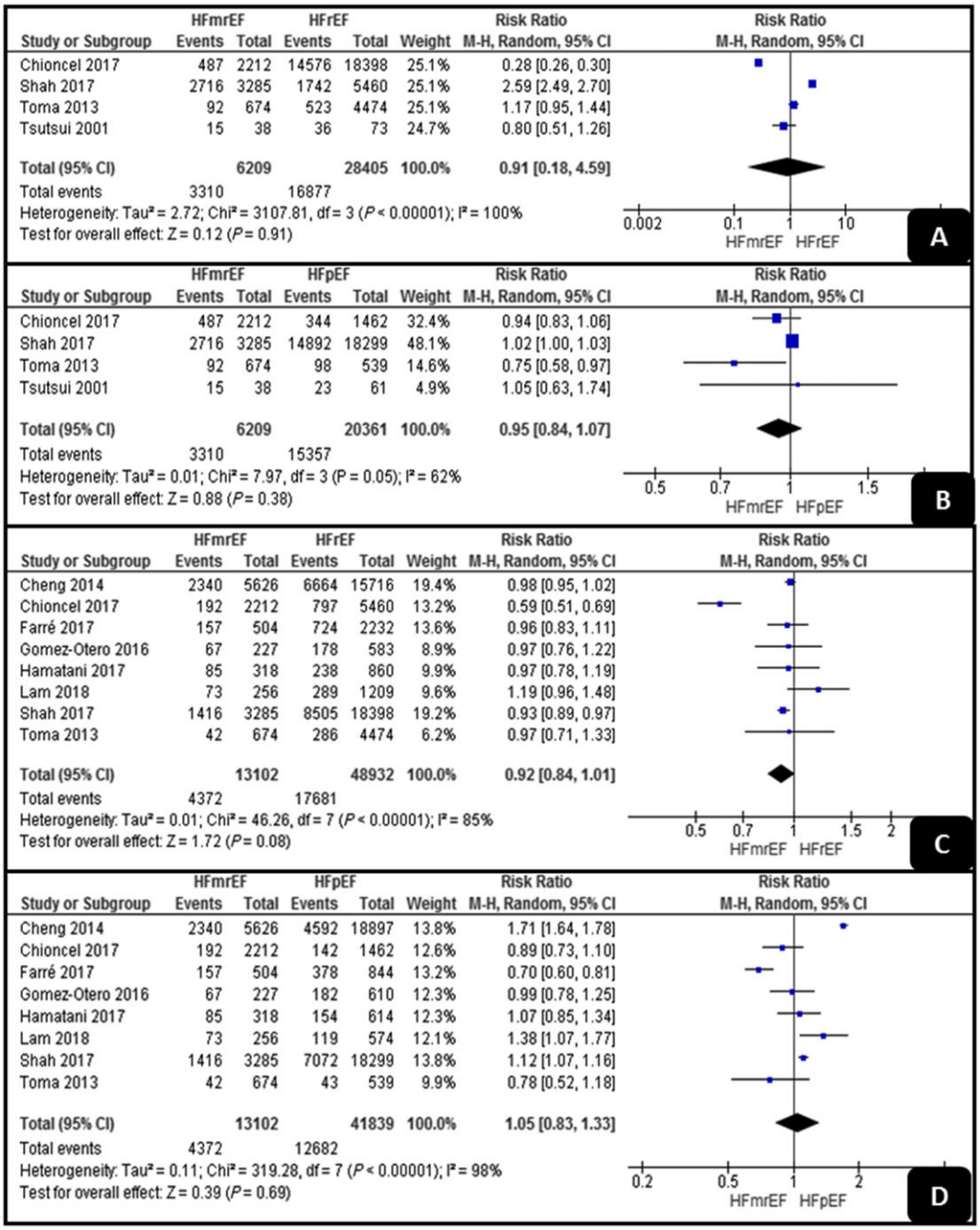
Figure 4 Forest plots demonstrating (A, B) all-cause hospitalization and (C, D) HF-related hospitalization. HFmrEF, mid-range ejection fraction heart failure; HFpEF, preserved ejection fraction heart failure; HFrEF, reduced ejection fraction heart failure.



and the measures of those outcomes did not show a high clinical significance.

Accordingly, we recommend developing other studies evaluating the cut-off points separating the HF subtypes. Future studies should consider the transition or the change of HF status over time as this may affect the outcomes. This could help prevent data overlap between the HF subtypes. Also, they should consider other factors affecting the outcomes such as distinguishing between acute and chronic HF and the data distribution inside each arm of HF.

Our study was limited by the marked level of heterogeneity across the studies, the different distribution of precipitating factors of HF possibly playing as confounders, the probably misleading values of RRs (which do not consider the different periods of follow-up), the type of HF (either

acute or chronic), and the similarity in the outcome between the three HF subtypes, but this may be explained as the eligible patients in some of the included studies belonged to the same medical centre and were of the same race, which raises the suspicion that their similar lifestyle and co-morbidities are the reason why they have similar mortality rates rather than being influenced by the subtype of HF they have. Also, 20 studies were eligible. Not all of them discussed the four outcomes as primary endpoints, so the small number of the data points made the outcome analysis less informative.

Conclusions

In conclusion, significant differences of hospitalization and mortality were detected between HFmrEF and the other subtypes of HF, which supports classifying HFmrEF as a special subtype.

Conflict of interest

None declared.

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